



The National Library of Medicine

175 Years of Advancing Biomedical Knowledge

Anita Slomski

IN 1968, THE PUBLISHER WILLIAMS & Wilkins sued the National Library of Medicine (NLM) for copyright infringement over the NLM's practice of sending other libraries single copies of journal articles at the request of researchers—a case reaching the US Supreme Court. In a split decision, the Supreme Court affirmed a lower court's decision that NLM's photocopying gave researchers necessary access to medical knowledge and did not violate copyright laws. No one then could envision how computer networks would change the way the world would access biomedical information.

Today, at the 175th anniversary of the NLM, the library's free access system PubMed processes nearly 1 billion online searches per year from users looking for medical and health information in more than 20 million articles published in more than 5300 journals. On the day in 1997 that the library's database of abstracts and articles became freely available to anyone with an Internet connection, Vice President Al Gore declared that PubMed “may do more to reform and improve the quality of health care in the United States than anything we have done in a long time.”

That was no exaggeration, says Donald A. B. Lindberg, MD, director of the NLM and a pioneer in the application of computers to medicine. When Lindberg came to the NLM in 1984 from the University of Missouri, where he was a professor of information science and pathology, “I had not imagined the Internet,” he recalled.

But to make PubMed possible, the NLM first had to create a vocabulary da-

tabase to enable computers to “read” the biomedical literature and patient records and appropriately categorize the meaning of different technologies and classifications. “We had to teach the computer that ‘heart’ and ‘cardiac’ are the same things,” said Lindberg, who

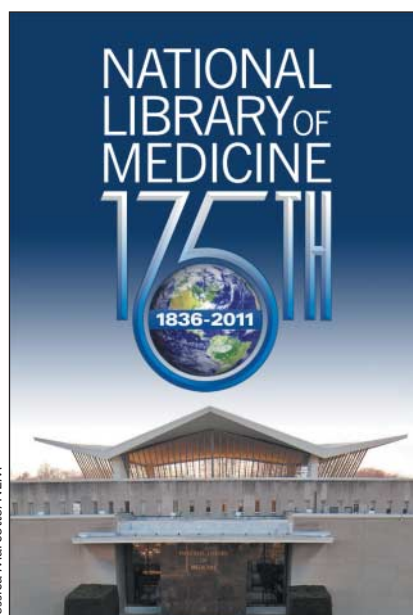
is the latest—and managing the deluge of biomedical information is an ever-present challenge.

“The area of scientific literature has broadened enormously since I came here,” Lindberg said. “HIV was totally unknown, women's health was not talked about, there was no Institute of Minority Affairs. The job of the National Library of Medicine is to acquire, organize, disseminate, and preserve the biomedical knowledge of the world for the benefit of public health. So we have to keep enlarging the set of journals we index and adding to the Unified Medical Language System in order to index it properly. And then we have to keep trying to understand it all.”

VISIBLE HUMAN

One of Lindberg's first charges as NLM director was to “watch carefully until the world had enough computing capacity to handle images and then to do something about that.” That “something” was the Visible Human, a digital image library of the complete anatomy of a man and a woman who each willed their body to science. The Visible Human male, consisting of magnetic resonance imaging, computed tomography, and anatomical images sectioned at 1-millimeter intervals, was released in 1994, followed 1 year later by the 3-dimensional, full-color images of the female, sectioned at one-third-millimeter intervals. Lindberg describes the project as “the best anatomical database since da Vinci.”

Lindberg said he expected Visible Human to be used mostly by medical schools, “to help students learn anatomy faster and maybe surgeons remember it longer,” since the database—



Jessica Marcotte/NLM

is on JAMA's editorial board. In 1990, after a 5-year effort, the NLM launched its Unified Medical Language System to index literature there and elsewhere, cementing the library's position as a leader in biomedical informatics.

From its modest beginnings in 1836 as a shelf with a handful of medical books that constituted the Library of the Office of the Surgeon General of the Army, the NLM has grown into the world's largest biomedical library. New librarian specialties have emerged with the growing body of scientific knowledge—disaster information specialist



unlike an actual cadaver—allows for repeated dissections without destroying the specimen. The Visible Human now has nearly 3200 licensees in 61 countries, and its applications include education, treatment planning, and artistic and mathematical use. The Visible Human data set also has applications in industry, such as building virtual crash dummies to be used in virtual cars for preliminary car design.

At a 1996 press conference, where the Visible Human was touted as “taking medical education out of the dark ages,” researchers showed off the ways they were using the computerized cadaver: rehearsing and planning for prostate surgery, visualizing the results of plastic and reconstructive surgery, and helping residents fine-tune their manual dexterity using an electronic scalpel on a computer screen.

Next-generation research promises to make the Visible Human even more realistic. Researchers at the University of Colorado are adding graphic, tactile, and acoustical interfaces to the Visible Human to give users the look, feel, and sound of real anatomy.

CLINICAL TRIALS REGISTRY

Before the NLM launched ClinicalTrials.gov in 2000, securing a spot in a clinical trial usually meant you had to know someone with clout. To make participating in clinical trials more democratic, a 1997 law included a provision for a public resource for information on drug trials for serious and life-threatening diseases, which led to the establishment of ClinicalTrials.gov. The intent was to enable patients to mine the registry for suitable trials. However, few sponsors of trials bothered registering them because the requirement to do so was not enforced.

The lack of a robust trials registry led to other, more serious problems. “There were studies that never saw the light of day if the drug sponsor didn’t want the results published or a journal editor rejected the paper,” said Deborah Zarin, MD, director of ClinicalTrials.gov. A notorious example is GlaxoSmith-Kline’s suppression of data on the safety

and efficacy of Paxil to treat depression in children, which came to light when the drug maker was sued for fraud in 2004 by then New York Attorney General Eliot Spitzer. In other cases, authors surreptitiously made changes to study protocols to enhance results for publication. A *JAMA* article on Celebrex, for example, showed a statistically significant difference between Celebrex and other drugs in the amount of gastrointestinal toxicity at 6 months. “It later became apparent that the pre-specified outcomes measure was 12 months,” said Zarin. “The authors had the data, which wasn’t statistically significant, so they never revealed it.”

Seeing that the government was not going to enforce registration of trials in ClinicalTrials.gov, the International Committee of Medical Journal Editors declared they would take matters into their own hands. Editors of key journals such as *JAMA* and the *New England Journal of Medicine* stated that, as of May 2005, they would refuse to publish articles about clinical trials of all interventions—not just drugs and devices—that had not been registered before enrolling participants. The policy had a huge impact. In the 7 months after the editors implemented the policy, “we went from having 25 to 30 trials registered per week to 250 trials registered each week,” says Zarin.

But the database continued to have gaps. In 2007, Congress added teeth to the original law, mandating registration of drug and device trials along with a summary of trial results—whether or not they were published in journals.

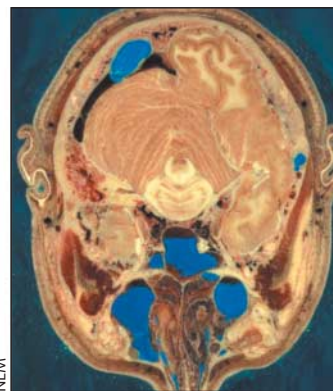
“About half of the studies in the results database have been published, so we have results from a large number of trials that people otherwise wouldn’t know about,” said Zarin. With more than 100 000 studies, ClinicalTrials.gov is not only the world’s largest clinical trials registry, but the only one with a results database.

“Over time, ClinicalTrials.gov will help practicing physicians by improving the validity and integrity of more metabolized sources of information, such as systematic reviews and practice guidelines,” said Zarin.

RESPONDING TO DISASTERS

When Hurricane Mitch devastated Nicaragua and Honduras in 1998, Congress asked the NLM to help. The initial response: “We’re a library, what can we do?” recalled Steven J. Phillips, MD, director of specialized information services for the NLM. After a meeting with public health officials in Central America, however, the answer became obvious—the NLM could provide real-time access to disaster health information to those managing the aftermath of the hurricane, while also helping officials collect and digitize the countries’ health data to rebuild public health infrastructures. The NLM has now created 10 disaster information centers in Central and South America, which provide computers, connectivity, and training on ways to access and collect vital health information in a disaster.

After an earthquake in Haiti in January 2010 destroyed the country’s health



The Visible Human, a digital image library of the complete anatomy of 2 individuals who each willed their body to science, has wide-ranging applications in medical education, treatment planning, industry, and other areas.



records, the NLM added mobile technology to track and disseminate disaster health information, such as cholera clinic locations and antibiotic inventories. "There are roughly 10 000 [nongovernmental organizations] in Haiti and they are each collecting data differently," said Phillips. "The NLM is helping them come up with a standard form so there can be a central repository of data."

The NLM is also a crucial presence during US disasters. After the terror attacks of September 11, 2001, for example, the NLM's National Center for Biotechnology Information (NCBI) developed software to analyze and organize DNA samples from the disaster site to help identify victims, said Phillips. The NLM has also created proactive disaster-management technology, such as a database containing information on 420 chemicals that can be downloaded to an emergency responder's handheld device. At the scene of a chemical spill, users can type in the characteristics of the chemical and find out what it is, what countermeasures to take, what protective gear to wear, and how to treat exposures. A similar technology, the Radiation Event Medical Management System, guides health care professionals on diagnosing and treating mass casualties during radiation or nuclear disasters.

For the last 3 years, the NLM has been lending its communications and information technology expertise to the Bethesda Hospitals' Emergency Preparedness Partnership, a model of how hospitals can collaboratively respond to a major disaster in the nation's capital. Three hospitals can together make available 600 beds in 8 hours to receive casualties. The NLM's role is to develop innovative methods to maintain communications among the hospitals if telephone and Internet access fail, such as rooftop lasers to transmit data and a dedicated fiberoptic network. The NLM is also charged with ensuring that hospital staff have necessary patient information, which would be supplied by technologies such as electronic triage recording computer

pens and radio-frequency identification systems for tracking patients and equipment bearing electronic tags.

The NLM is now making plans to export its disaster response template to other hospitals around the country. Phillips noted that participation in such a response system would require monetary support of about \$2 million per city. "Hospitals can't afford to isolate beds, have staff on call, and keep equipment in a warehouse on their own," he said.

THE HUMAN GENOME

When members of the Human Genome Project announced in 2000 that they would be sequencing a working draft of the human genome, the quantity of data the NLM was asked to house was staggering. "Three billion nucleotides—how would you even store that amount of data?" Lindberg marveled. But the library had faced that issue before with the Visible Human project. Alvy Ray Smith, PhD, cofounder of Pixar and head of computer graphics research for Lucasfilm, was on the NLM's board of regents at the time. He told Lindberg, "You do the medical part and the engineers will have something for you to put it on, don't worry."

This time, NCBI investigators created numerous databases to offer the world a one-stop resource for genomic information. GenBank, for example, stores the sequence data of the Human Genome Project, and the Database of Genotypes and Phenotypes

(dbGaP) was developed to make available the results of genome-wide association studies that examine the interactions between genes and traits.

Building the dbGaP database was monumental. "No two epidemiologic studies are designed the same, and phenotypes are particularly tricky to catalog, since measurements such as blood pressure can be taken a number of different ways," explained Jim Ostell, PhD, chief of NCBI's information engineering branch. What staff had to do was to incorporate the text of each study's instructions to physicians on how to take various measurements—often printed on paper—and link it to each data element in the study.

"There are also many political and social issues having to do with patient privacy and consent in sharing these types of data, so we were an active party in establishing the conventions and ethical basis for depositing the data and gaining access to them," said Ostell.

The database has changed the way researchers do genome-wide association studies, Ostell said. "By combining a study on, say, macular degeneration with Framingham's cardiac data, researchers can find patterns of genetic markers associated with high blood pressure and macular degeneration, for instance, without having to do physical exams on another 500 people and genotyping them," said Ostell.

Researchers are also building on the database. "If you have DNA from pre-



ClinicalTrials.gov, a registry of clinical trials launched by the National Library of Medicine, is the world's largest clinical trials registry and the only such database to include summaries of trial results.



vious genome-wide association studies, you can apply newer technology, such as targeted sequencing, without having to recreate 20 years of someone's health history in order to get better genetic information," said Ostell.

Twenty-five years ago, NLM director Lindberg had no way of knowing that the Internet would deliver the NLM's vast holdings of biomedical information to an equally impressive number of people. But he has envisioned how the next 20 years will bring advances in natural language recognition such that "computers in the future will be able to understand the scientific literature" instead of merely

"reading" it with the help of a human indexer. "Computers are only meeting us halfway now in medical indexing," Lindberg said. Another reasonable expectation is for information systems to comprehend the patient record and search through it in order to give every patient a link to MedlinePlus, NLM's health Web site that explains 800 diseases and conditions.

That immediate connection to information can be a powerful way to educate patients about their diagnoses and complications, said Lindberg. "I'd like to see us link to MedlinePlus from the electronic medical record as part of every hospital discharge," he said. □

Study: Up to 1 in 10 Infants Given Herbal Supplements, Teas by Their Mother

Rebecca Voelker

A RECENT STUDY HAS ALERTED US physicians that many of the infants in their care are given potentially harmful herbal supplements and teas.

Researchers from the US Food and Drug Administration (FDA) and University Hospitals Case Medical Center in Cleveland reported data from the Infant Feeding Practices Study II showing that about 9% of infants receive supplements or tea during their first year of life (Zhang Y et al. *Pediatrics*. doi:10.1542/peds.2010-2294 [published online ahead of print May 2, 2011]).

The data are based on questionnaire responses from 2653 healthy mothers who gave information about their pregnancy and their child's first year of life. The questionnaires were distributed nationally but results are not considered nationally representative because some ethnic groups were underrepresented in the study population.

In the survey, mothers reported giving their infant a wide variety of supplements and teas. Those most com-

monly used included gripe water (an herbal preparation given for colic), chamomile, teething tablets, and unspecified types of tea.

Mothers were more likely to give their infant a supplement or tea if they used the products themselves, had only 1 child, were aged 35 years or older, had attended college, had incomes at or above 350% of the poverty level, and lived in the Western part of the United States. Hispanic mothers were more likely than white mothers to give their infant a supplement or tea.

The most common reasons mothers gave for using the products were to appease fussy infants, as a digestion aid, to relieve colic, and to help their infant relax. Many of the products were marketed and sold specifically for infants, according to the study.

Supplements and tea are not regulated in the same way as pharmaceuticals, the authors noted. Therefore, they could contain potentially harmful contaminants or heavy metals, and some could also cause adverse effects if given while an infant is taking medication. □

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Questioning Salt Restriction

National policies aimed at restricting sodium intake may not provide the anticipated cardiovascular benefits and could be detrimental to health.

Of 3681 study participants, those with the lowest sodium intake at the beginning of the 8-year trial were significantly more likely than others who consumed more sodium to die of cardiovascular disease. All participants had the same risk of developing hypertension, regardless of initial sodium intake.

<http://tinyurl.com/6hgr6zx>

"Pragmatic" Asthma Approach

In rigorous randomized, controlled trials, inhaled glucocorticoids emerged as the preferred first step in treating asthma. But in the real world, where patients do not meet strict research



Ted Grudzinski/AMA

criteria, new research shows that leukotriene-receptor antagonists (LTRAs) may be just as effective as first-line treatment.

Investigators who studied patients in primary care practices said LTRAs have practical advantages. Taking the pills is easier than using an inhaler. As a result, patients are more likely to reliably take their medication.

<http://tinyurl.com/3zt9qv6>

Obesity Screening at Age 2

Children as young as 2 years had more weight-loss success in a clinical obesity program than older children, new research shows. The findings, say investigators, should prompt a revision in national guidelines to decrease the age for initiating screening of children for obesity to age 2 years. The US Preventive Services Task Force, an independent group that develops national screening guidelines, says obesity screening should begin at age 6 years.

<http://tinyurl.com/3b97j8y>

Vulnerable to PTSD

Military service personnel serving in Iraq or Afghanistan were more likely to develop post-traumatic stress disorder (PTSD) if they had a mental health disorder before deployment or if they were physically injured while deployed, according to new findings.

Compiling health status questionnaires before deployment may help identify those military personnel who are most vulnerable to developing PTSD symptoms, the study authors suggested.

<http://tinyurl.com/3wyyhkg>

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